(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/034006 A1

(51) International Patent Classification:
C07C 317/48 (2006.01) *A61K 31/277* (2006.01)

(21) International Application Number:
PCT/US2005/033074

(22) International Filing Date:
16 September 2005 (16.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PCT/US2004/030442	17 September 2004 (17.09.2004)	US
10/943,768	17 September 2004 (17.09.2004)	US
60/664,244	21 March 2005 (21.03.2005)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/034006 A1

(54) Title: POLYMORPHS OF THE CYSTEINE PROTEASE INHIBITOR N- (1-CYANOCYCLOPROPYL)-3-CYCLOPROPYLMETHANSULFONYL-2 (R) - (2,2,2-TRIFLUORO-1 (S) - (4-FLUOROPHENYL) ETHYLAMINO) PROPIONAMIDE

(57) Abstract: The present invention is directed to polymorphs of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide, methods of using them to treat a disease mediated by cathepsin S, pharmaceutical compositions comprising such polymorphs, and processes for preparing them.

POLYMORPHS OF THE CYSTEINE PROTEASE INHIBITOR N-(1-CYANOCYCLOPROPYL)-3-CYCLOPROPYLMETHANSULFONYL-2(R)-(2,2,2-TRIFLUORO-1(S)-(4-FLUOROPHENYL)ETHYLAMINO) PROPIONAMIDE

Field of the Invention

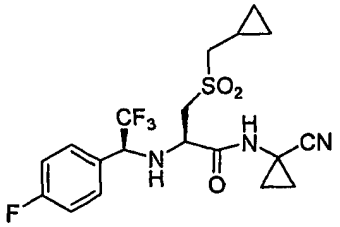
The present invention is directed to polymorphs of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionamide, methods of using them to treat a disease mediated by cathepsin S, pharmaceutical compositions comprising such polymorphs, and processes for preparing them.

State of the Art

Polymorphs are crystals of the same molecule having different physical properties as a result of the order of the molecules in the crystal lattice. The differences in the physical properties exhibited by polymorphs can affect the pharmaceutical properties of a drug such as storage stability, compressibility and density which is important in formulation and manufacturing, and solubility/dissolution rates that can in turn affect the bioavailability of a drug. As a result of solubility/dissolution differences, in some cases, polymorphoic transitions can result in lack of potency and/or toxicity. Therefore, the Food and Drug Administration requires tight controls on the polymorphoic content of the active component in solid dosage forms. In general, if a marketed drug exists in polymorphic forms having different stabilities the regulatory agency requires batch-by-batch monitoring of such drugs for quality assurance. Therefore, it is preferred for both medical and commercial reasons to produce and market the pure drug in its most thermodynamically stable polymorph. However, the less thermodynamically stable polymorphs may also be useful as intermediates that may be converted to the more stable polymorph. The present invention fulfills this and related needs.

SUMMARY OF THE INVENTION

N-(1-Cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide having the structure:



and hereinafter referred to as the compound of Formula (I) can exist in three different crystalline polymorphic forms referred to herein as Forms A, B, and C, and an amorphous

form referred to herein as Form D, Form A being the most thermodynamically stable.

Accordingly, in one aspect, the present invention is directed to a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 19.47, and 21.67° (2-theta) and is referred to herein as Form A.

In a second aspect, the present invention is directed to a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having a characteristic peak at about 5.65° (2 theta) and is referred to herein as Form B.

In a third aspect, the present invention is directed to a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.24 and 7.50° (2-theta) and is referred to herein as Form C.

In a fourth aspect, the present invention is directed to a compound of Formula (I) having an amorphous form which exhibits an X-ray powder diffraction pattern having broad peaks, between about 5 and 12 and about 14 and 25° (2-theta) and is referred to herein as Form D.

In a fifth aspect, this invention is directed to a pharmaceutical composition comprising a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 19.47, and 21.67° (2-theta) (Form A) and a pharmaceutically acceptable excipient. Preferably, a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 8.52, 9.15, 14.42, 17.67, 18.79, 19.47, 19.74, 21.67, 23.16, 23.89, 25.31, and 27.06° (2-theta); and FT-IR spectrum with peaks at about 704, 731, 777, 791, 808, 822, 837, 892, 921, 935, 987, 1008, 1028, 1053, 1080, 1115, 1128, 1161, 1180, 1230, 1261, 1288, 1361, 1418, 1465, 1513, 1548, 1607, 1663, and 3349 cm^{-1} (Form A) and a pharmaceutically acceptable excipient. Preferably, a pharmaceutical composition comprising a compound of Formula (I) that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 19.47, and 21.67° (2-theta) (Form A) and a pharmaceutically acceptable excipient. More preferably, Form A is present in greater than 80% purity. Even more preferably, in greater than 90% purity. Even more preferably, Form A is present in greater than 95% purity.

In a sixth aspect, this invention is directed to a pharmaceutical composition comprising a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peak at about 5.65° (2 theta) (Form B) and a pharmaceutically acceptable excipient. Preferably, a pharmaceutical composition comprising a

compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 5.65, 6.68, 10.12, 18.63, 19.40, 20.66, 21.47, 21.93, 22.47, 23.78, 25.52, 25.76, and 26.79° (2-theta) and FT-IR spectrum peaks at about 704, 731, 791, 808, 823, 837, 856, 893, 936, 1028, 1053, 1080, 1115, 1128, 1161, 1180, 1230, 1287, 1361, 1418, 1465, 1514, 1548, 1607, 1663, and 3349 cm^{-1} (Form B) and a pharmaceutically acceptable excipient. More preferably, a pharmaceutical composition comprising a compound of Formula (I) that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peak at about 5.65° (2 theta) (Form B) and a pharmaceutically acceptable excipient. Even more preferably, Form B is present in greater than 80% purity. Even more preferably, in greater than 90% purity. Even more preferably, Form B is present in greater than 95% purity.

In a seventh aspect, this invention is directed to a pharmaceutical composition comprising a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.24 and 7.50° (2-theta) (Form C) and a pharmaceutically acceptable excipient. More preferably a pharmaceutical composition comprising a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction having peaks at having peaks at about 6.24, 7.50, 17.68, 18.76, 19.80, 21.86, 23.93, and 25.28° (2-theta). Preferably, a pharmaceutical composition comprising a compound of Formula (I) that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.24 and 7.50° (2-theta) (Form C) and a pharmaceutically acceptable excipient. More preferably, Form C is present in greater than 80% purity. Even more preferably, in greater than 90% purity. Even more preferably, Form C is present in greater than 95% purity.

In an eighth aspect, this invention is directed to a pharmaceutical composition comprising a compound of Formula (I) having a polymorphic form which exhibits an X-ray powder diffraction pattern having broad peaks between about 5 and 12 and about 14 and 25° (2-theta) (Form D) and a pharmaceutically acceptable excipient. Preferably, a pharmaceutical composition comprising a compound of Formula (I) that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having broad peaks between about 5 and about 12 and 14 and 25° (2-theta) (Form D) and a pharmaceutically acceptable excipient. More preferably, Form D is present in greater than 80% purity. Even more preferably, in greater than 90% purity. Even more preferably, Form D is present in greater than 95% purity.

In a ninth aspect, this invention is directed to a method of treating a disease in an animal which is mediated by Cathepsin S which method comprises administering to the animal

any of the pharmaceutical compositions described above. Preferably, the animal is human and the disease is juvenile onset diabetes, psoriasis, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis, Hashimoto's thyroiditis, allergic disorders including, but not limited to, asthma, allogeneic immune responses including, but not limited to, organ transplants or tissue grafts and endometriosis, chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, chronic pain, cancer, pneumonities and cardiovascular disease such as plaque rupture and atheroma, systemic amyloidosis, Alzheimer's disease, and iatrogenic disorders.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is an X-ray powder diffraction (XRPD) of the compound of Formula (I) Form A.

FIG. 2 is a Fourier infrared spectroscopy (FT-IR) of the compound of Formula (I) Form A.

FIG. 3 is an X-ray powder diffraction (XRPD) of the compound of Formula (I) Form B.

FIG. 4 is a Fourier infrared spectroscopy (FT-IR) of the compound of Formula (I) Form B.

FIG. 5 is an X-ray powder diffraction (XRPD) of the compound of Formula (I) Form C.

FIG. 6 is an X-ray powder diffraction (XRPD) of the compound of Formula (I) Form D.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings:

A "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet

experience or display symptoms of the disease;

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound of Formula (I) that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

"Substantially pure" when used in reference to a polymorphic form of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide i.e., compound of Formula (I) refers to a polymorphic form of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide which is about 80% pure, preferably from about 85 to about 95 pure, even more preferably from about 98 to about 99.9% pure. This means that the amount of other polymorphic form(s) of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethane-sulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide present is(are) not more that about 20%, preferably not more than about 15 to about 5%, even more preferably not more than about 2 to about 0.1%.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

"Sufficient chemical affinity" when used in reference to a solvent or solvent mixture refers to a solvent or solvent mixture having the capability of dissolving the compound of Formula (I) in an amount to enable crystallization of the compound. This capability may be a function of the temperature or may vary with different polymorphs of the compound.

"Mechanical stress" when used herein in reference to a processing step means that the compound of Formula (I) is subjected to a mechanical force or a change (reduction or increase) of mechanical force such as a shear force and includes filtration, capillary action, ultrasound, particle size changes, such as grinding, milling, micronizing, stirring, drying, sublimation or removal of solvent, and other mechanical force exposures described herein in more detail.

One of ordinary skill in the art will appreciate that an X-ray diffraction pattern may be obtained with a measurement error that is dependent upon the measurement conditions employed. In particular, it is generally known that intensities in an X-ray diffraction pattern may fluctuate depending upon measurement conditions employed. It is further understood that relative intensities may also vary depending upon experimental conditions and, accordingly,

the exact order of intensity should not be taken into account. Additionally, a measurement error of diffraction angle for a conventional X-ray diffraction pattern is typically about 5% or less, and such degree of measurement error should be taken into account as pertaining to the aforementioned diffraction angles. Consequently, the term "about" when used herein in reference to X-ray powder diffraction patterns means that the crystal forms of the instant invention are not limited to the crystal forms that provide X-ray diffraction patterns completely identical to the X-ray diffraction patterns depicted in the accompanying Figures disclosed herein. Any crystal form that provides X-ray diffraction patterns that is substantially identical as to those disclosed in the accompanying Figures fall within the scope of the present invention. The ability to ascertain whether the polymorphic forms of a compound are the same albeit the X-ray diffraction patterns are not completely identical is within the purview of one of ordinary skill in the art. The same is true when determining the polymorphic form using the FT-IR spectra disclosed herein i.e., any crystal form that provides FT-IR spectrum that is substantially identical as to those disclosed in the accompanying Figures fall within the scope of the present invention.

The terms "without substantially affecting the integrity of the compound" when used herein in reference to a processing step means that the chemical identity of the compound of Formula (I) is not significantly altered after completion of the processing step; in other words chemical bonds remain substantially intact.

The term "without substantially affecting the two asymmetric centers of the compound" means that after the completion of the process of preparing a polymorph the optical configuration of the two asymmetric centers is retained at least to about 90%, preferably to about 95% or above.

"Liquefaction" when used in reference to the compound of Formula (I) means conversion of the compound into liquid form or melting.

Bioavailability, the ability to process, and stability of the product are influenced by the existence of varied physical and chemical properties of the solid-state forms associated with the various polymorphs. Although polymorphs of the invention have the same elemental composition, they exhibit different physico-chemical and physico-technical properties such as free energy, entropy, heat capacity, melting point, sublimation temperature, solubility, stability, dissolution rate, bioavailability, hardness, compatibility, flowability, tensile strength and compressibility, all of those being factors to determine the suitability of a polymorph for its pharmaceutical use. While the thermodynamically most stable polymorph is generally the preferred choice for marketing, other polymorphs of an active ingredient may also play an

important role, not only in drug quality assurance monitoring. For example, the less stable polymorphs can be used as important intermediates to prepare the more stable polymorph.

Characterization of the polymorphic forms of compound (I):

The polymorphic forms of compound (I) were characterized by melting point, X-ray powder diffractometry (XRPD) and Fourier Transform Infrared Spectroscopy (FT-IR). The X-ray diffraction (XRPD) analyses were performed using an Inel XRG-3000 diffractometer equipped with a CPS (Curved Position Sensitive) detector with a 2θ range of 120°. Real time data were collected using Cu-Kα radiation starting at approximately 4° 2θ at a resolution of 0.03° 2θ. The tube voltage and amperage were set to 40 kV and 30 mA, respectively. The pattern was displayed from 2.5-40° 2θ. Samples were prepared for analysis by packing them into thin-walled glass capillaries. Each capillary was mounted onto a goniometer head that is motorized to permit spinning of the capillary during data acquisition. The samples were analyzed for 5 or 10 min. Instrument calibration was performed using a silicon reference standard.

Infrared spectra were acquired on a Magna-IR 860® Fourier transform infrared (FT-IR) spectrophotometer (Thermo Nicolet) equipped with an Ever-Glo mid/far IR source, an extended range potassium bromide (KBr) beamsplitter, and a deuterated triglycine sulfate (DTGS) detector. An attenuated total reflectance (ATR) accessory (the Thunderdome™, ThermoSpectra-Tech) with a germanium (Ge) crystal was used for data acquisition. Samples were analyzed neat. Each spectrum represents 256 co-added scans collected at a spectral resolution of 4 cm^{-1}. A background data set was acquired with a clean Ge crystal. A Log $1/R$ (R = reflectance) spectrum was acquired by taking a ratio of these two data sets against each other and was then converted to Kubelka-Munk units. Wavelength calibration was performed using polystyrene. A background data set was acquired on a sample of KBr.

Form A:

Form A is an anhydrous, non-hygroscopic, crystalline material with a melting point at about 175 °C. The XRPD of Form A is shown in FIG. 1 having peaks at about 6.19, 8.52, 9.15, 14.42, 17.67, 18.79, 19.47, 19.74, 21.67, 23.16, 23.89, 25.31, and 27.06° (2-theta). The unique peaks for Form A in XRPD are at about 6.19, 19.47, and 21.67° (2-theta). The FT-IR spectrum of Form A showed peaks at about 704, 731, 777, 791, 808, 822, 837, 856, 892, 921, 935, 987, 1008, 1028, 1053, 1080, 1115, 1128, 1161, 1180, 1230, 1261, 1288, 1361, 1418, 1465, 1513, 1548, 1607, 1663, and 3349 cm^{-1}.

Form B:

Form B is a solvate and maybe a hydrate. The XRPD of form B is shown in FIG. 3

having peaks at about 5.65, 6.68, 10.12, 18.63, 19.40, 20.66, 21.47, 21.93, 22.47, 23.78, 25.52, 25.76, and 26.79° (2-theta). The unique peak for Form B in XRPD is at about 5.65° (2-theta). The FT-IR spectrum of Form B showed peaks at about 704, 731, 791, 808, 823, 837, 856, 893, 936, 1028, 1053, 1080, 1115, 1128, 1161, 1180, 1230, 1287, 1361, 1418, 1465, 1514, 1548, 1607, 1663, and 3349 cm^{-1}.

Form C:

Form C is anhydrous. The XRPD of form C is shown in FIG. 5 having peaks at about 6.24, 7.50, 17.68, 18.76, 19.80, 21.86, 23.93, and 25.28° (2-theta). The unique peaks for Form C in XRPD are at about 6.24 and 7.50° (2-theta).

Form D:

Form D is amorphous and has XRPD shown in FIG 6 with broad peaks, between about 5 and 12 and about 14 and 25° (2-theta).

Detailed syntheses of Forms A-D are provided in working examples below.

XRPD Peaks (°2θ) and Relative Intensity Listing for Forms A, B, C, and D are listed in Table 1 below:

Table 1

Form A		Form B		Form C		Amorphous
°2 θ	I/I_1	°2 θ	I/I_1	°2 θ	I/I_1	Broad peak between (°2 θ):
6.19	100	5.65	100	6.24	100	5 and 12
8.52	9	6.68	9	7.50	67	14 and 25
9.15	6	10.12	10	17.68	26	
14.42	8	18.63	39	18.76	39	
17.67	6	19.40	22	19.80	14	
18.79	21	20.66	13	21.86	45	
19.47	13	21.47	32	23.93	19	
19.74	8	21.93	25	25.28	23	
21.67	32	22.47	14			
23.16	10	23.78	18			
23.89	16	25.52	14			
25.31	12	25.76	12			
27.06	7	26.79	10			

Unique XRPD Peaks for Forms A, B, and C (no other peaks within ± 0.20 °2θ make up a unique set for each crystalline form) are listed in Table 2 below:

Table 2

Form A °2θ	Form B °2θ	Form C °2θ
6.19	5.65	6.24
19.47		7.50
21.67		

IR Peak Listing for for Forms A, B, C, and D: (peaks > 400 cm^{-1}) are listed in Table 3 below:

Table 3

Peak Positions in Wavenumbers (cm^{-1})			
Form A		Form B	
704	1115	704	1230
731	1128	731	1287
777	1161	791	1361
791	1180	808	1418
808	1230	823	1465
822	1261	837	1514
837	1288	856	1548
856	1361	893	1607
892	1418	936	1663
921	1465	1028	3349
935	1513	1053	
987	1548	1080	
1008	1607	1115	
1028	1663	1128	
1053	3349	1161	
1080		1180	

Processes for Preparing the Polymorphs of the Invention

A description of various processes for preparing polymorphs can be found in the article 'New Trends in the Crystallisation of Active Pharmaceutical Ingredients' by S. Banga *et al.*, October 2004 in Business Briefings *PharmaGenerics* 2004, p. 70 and the literature reported in that article.

The different polymorphs of the invention may be produced by solvent crystallization or non-solvent crystallization. The different methods of crystallization generate different crystal forms by providing varied reaction conditions. Crystallization from solution (single solvent or solvent mixtures) and non-solvent methods such as sublimation, thermal treatment, desolvation, processing (grinding) and crystallization from melting are the commonly used methods. Capillary crystallization, laser-induced crystallization and sonocrystallization target the nucleation stage to enhance the crystallization rate.

The existence of different polymorphs obtained by using the various methods can be ascertained by using thorough and rapid polymorph screens known in the art. The most convenient process of preparing the polymorphs involves crystallization from a solvent.

Solvent Crystallization

Meticulous consideration of the factors affecting solvent recrystallization like solvent polarity, addition of a non-solvent, degree of supersaturation, temperature along with the cooling profile, additives, seeds, pH and agitation rate aids in elucidating the complete

polymorphic picture of the active ingredient. Suitable solvents are solvents that have sufficient chemical affinity for the compound of the invention and do not substantially affect the two asymmetric centers of the molecule during the crystallization process. These include lower alkanols with 1 to 6 carbon atoms, such as ethanol or 2-propanol etc., ketones with 3-6 carbon atoms such as acetone, methyl ethyl ketone, etc., halogenated hydrocarbons with 1 to 4 carbon atoms, such as methylene chloride, 1,1-dichloroethane, etc., aqueous solvents, such as mixtures of water with lower alkyl nitriles, such as acetonitrile, propionitrile, and the like and aromatic solvents with 6 to 8 carbon atoms such as benzene, toluene, or xylenes, etc. and suitable mixtures of these solvents. In general, a mixture of the solvent with the compound of Formula (I) will be heated to an elevated temperature between 40 °C to 100 °C, preferably 50 to 90 °C. After the selected higher temperature is reached and the compound is in solution commonly at about saturation concentration, the solution will be cooled down slowly. Often it is useful to control the cooling with a cooling rate between 0.5 to 10 °C/ h, preferably 1 to 8 °C/h, most preferably 1 to 5 °C/h. For certain solvents it may be preferred to allow slow evaporation of the solvent, for example with acetone. In that case it may not be necessary to start the crystallization step with a saturated solution of the compound of Formula (I). Often filtering of the hot solution through a preheated filtering device may be useful to remove impurities. The isolated compound will be allowed to dry and its polymorphic form be determined by one of the methods herein described. Solvent crystallization is preferred for the preparation of the more stable polymorphs, in particular the most stable polymorph (for example, Form A).

For metastable Forms B and C certain selected solvents may be used, for example, halogenated lower alkanols, preferably perhalogenated alkanols with 2 to 6 carbon atoms, most preferably trifluoroethanol. The more preferred methods for obtaining Form C are non-solvent crystallizations, such as sublimation, thermal treatment, desolvation, processing (grinding), sonication such as electrosonication or laser-induced crystallization may be suitable.

Newer crystallization strategies, such as laser-induced crystallization, capillary crystallization and sonocrystallization, target the nucleation stage. These techniques, by use of unusual reaction conditions or mechanical stress (e.g. ultrasound and laser as a source of energy), are often helpful in the screening process and for preparing different polymorphs of the compound of Formula (I), in particular thermodynamically less stable polymorphs. These techniques are comprehensive and are accompanied by enhanced crystallization rates. Ascertaining the metastable forms through a capillary environment can prove to be of assistance. The scalability advantage of sono-crystallization and laser-induced crystallization certainly has good prospects. In addition, sonocrystallization can be effectively utilized to

reduce the particle size.

Capillary Crystallization

This technique uses capillary tubes as crystallization vessels and captures metastable forms of the active ingredient by manipulating the metastable zone width. In the conventional regimen metastable forms having greater solubility tend to dissolve and the stable form crystallizes out at the expense of it. A capillary environment possessing a small volume of solution with reduced convection and low turbulence is ideal for the isolation of alternative less stable forms. The capillary system technique allows a slow evaporation rate, thereby prolonging the metastable zone and generating high concentration enough for the solution to be supersaturated relative to the metastable phases. The careful selection of evaporation conditions is often important to obtain the metastable form.

Laser-induced Crystallization

Lasers are a form of electromagnetic radiation, characterized by an oscillating electric field. They produce light at different wavelengths in visible, infrared and ultraviolet regions of the spectrum in both continuous and pulsed format. Laser–induced crystallization makes use of solid-state lasers, particularly the Q-switched neodymium yttrium aluminium garnet (Nd:YAG) laser, which generates intense pulses in the near infrared region. It is characterized by continuous output of a few tens of watts to 1,800W. An apt way for crystallization to take place is to employ a pulsed source, which acts for few nanoseconds. Laser pulses predominantly act on the pre-existing clusters, thereby assisting in the organization of the pre-nucleating clusters and embryos into nuclei. The basic principle of laser-induced crystallization involves the induction of a dipole moment in molecules by the oscillating electric field. The same field then interacts with the induced dipole, applying a torque to the molecules and aligning them along the most polarizable axis parallel to the field. The general methodology applicable for laser-induced crystallization starts with the preparation of a saturated solution at a specific temperature in pyrex screw-capped test tubes. Supersaturation is achieved either by temperature cycling for several days or by sonication. The solution is then cooled slowly to room temperature and held at the same temperature for a few days. The aging allows enrichment of the cluster size and number, thus improving the probability of nucleation. The solution is then illuminated with high-energy laser pulses (Nd:YAG laser oscillator amplifier system) showing the appearance of macroscopic crystals within seconds.

Sonocrystallization

Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. It not only enhances the nucleation rate, but is also an

effective means of size reduction and controlling size distribution of the active ingredient. The technique proves to be a good alternative to mechanical size reduction, which may be accompanied by polymorphic transformations. It can be promising in the crystallization of an active ingredient to be formulated for inhalation purposes, which requires an active ingredient in size-reduced form. Sonic waves exert alternate cycles of compression and rarefaction within a liquid, creating bubbles during the rarefaction stage. These bubbles survive repeated cycles of compression and rarefaction until a critical size is reached, and then collapse to form cavities. This process is known as cavitation. The phenomenon of cavitation provides energy, stimulating a rise in temperature. This modest rise in temperature as a result of cavitation in a saturated solution is capable of accelerating nucleation many times. Experimentally, sonic waves with a power above 10W are applied in a continuous mode via a probe in the saturated solution, mixed with an anti-solvent. Enhancement in the nucleation rate is detected visually by the time taken to deposit the solid. Care needs to be taken to prevent that sonic waves of too high energy do not break bonds leading to degradation of the active ingredient.

Grinding Methods:

Grinding will often be carried out with mixing-milling equipment either at room temperature or temperatures below room temperature, sometime at temperatures down to about – 200 °C, approximately the boiling point of liquid nitrogen for 10 to 60 minutes, more preferably 15 to 45 minutes. After the grinding step is completed the sample will be allowed to warm up to room temperature.

Amorphous polymorphs may be prepared by liquefaction of the compound of Formula (I), for example by heating the compound to a temperature above its melting point, followed by rapid cooling. The rapid cooling of the melt prevents crystallization. Alternatively, amorphous polymorphs may be prepared by particle size reduction at temperature significantly below room temperature, for example at about -200 °C.

Utility and Testing

Polymorphs of the compound of Formula (I) are selective inhibitors of cathepsin S, and accordingly are useful for treating diseases in which cysteine protease activity contributes to the pathology and/or symptomatology of the disease. For example, the polymorphs of the invention are useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, psoriasis, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders, including, but not limited to, asthma, allogeneic immune responses, including, but

not limited to, organ transplants or tissue grafts and endometriosis.

Cathepsin S is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

The Cathepsin S inhibitory activity of the polymorphs of compound of Formula (I) can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Details of assays for measuring Cathepsin S inhibitory activity are set forth in Biological Examples 1 and 2, *infra*.

Administration and Pharmaceutical Compositions

In general, the polymorphs of the compound of Formula (I) will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula (I) may range from about 10 micrograms per kilogram body weight (μg/kg) per day to about 100 milligram per kilogram body weight (mg/kg) per day, typically from about 100 μg/kg/day to about 10 mg/kg/day. Therefore, a therapeutically effective amount for an 80 kg human patient may range from about 1 mg/day to about 8 g/day, typically from about 1 mg/day to about 800 mg/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula (I) for treating a given disease.

The polymorphs of compounds of Formula (I) can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula (I) in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient.

Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

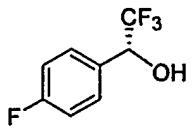
The amount of a polymorph of the compound of Formula (I) in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a polymorph of compound of Formula (I) for treating a given disease will comprise from 0.01%w to 90%w, 5%w to 50%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a polymorph of compound of Formula (I) are described in Example 1 below.

Examples

All solvents and reagents were purchased from Aldrich and used as received except where noted. All reactions and products were analyzed for chemical purity using reverse-phase HPLC. Moisture content of reaction products and reagents were determined using an EM-Science model V-200 AQUASTAR volumetric Karl Fischer titrator. Combustion analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

Reference A

Synthesis of 2,2,2-trifluoro-1(*R*) -(4-fluorophenyl)ethanol

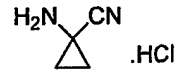


To a 2L, 3-neck round-bottom flask fitted with a thermometer, mechanical stirrer, stir-

shaft and teflon stir-blade, was added 2,2,2,4'-tetrafluoroacetophenone (80.0 g, 0.416 mol) and anhydrous dichloromethane (320 mL). The flask was flushed with nitrogen then cooled to -78 °C by means of a dry ice/acetone bath. To the resulting solution was added 1-(*S*)-methyl-CBS oxazaborolidine (41 mL, 1.03 M solution in toluene, 0.042 mol). Catecholborane (249 g as a 2M solution in toluene; purchased from BASF) was added dropwise at a rate to maintain an internal temperature below -75 °C. After the addition was complete, the reaction mixture was stirred overnight at -75 °C for ~15 h and then quenched by slow addition of 4N HCl in 1,4-dioxane (31 mL; 0.124 mol), maintaining the internal temperature below -75 °C. The ice bath was removed and the reaction mixture allowed to warm up to room temperature over a 3 h period. The reaction mixture was concentrated to a final volume of ~200 mL to afford a white suspension. Hexane (800 mL) was added and the suspension filtered. The filtrate was washed with water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* at a water bath temperature of 30-35 °C and pressure of 5 mbar to afford 2,2,2-trifluoro-1(*R*) -(4-fluorophenyl)ethanol (67 g) as a reddish oil. Analysis of the product by chiral HPLC showed this to be a 95:5 mixture of *R*- and *S*-isomers corresponding to an enantiomeric excess of 90%.

Reference B

Synthesis of 1-aminocyclopropanecarbonitrile hydrochloride



Step 1

A mixture of benzophenone imine (25 g, 0.138 mol, Aldrich) and aminoacetonitrile hydrochloride (25 g, 0.270 mol, Lancaster) in dichloromethane (1000 mL) was stirred in a 2L Erlenmeyer flask under nitrogen at room temperature for 5 days. The reaction mixture was filtered to remove the precipitated ammonium chloride and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was dissolved in ether (400 mL) washed with water (200 mL) and brine. After drying over magnesium sulfate the solvents were evaporated to give (benzhydrylideneamino)acetonitrile (47.89 g).

Step 2

A solution of sodium hydroxide (91 g, 2.275 mol) in water (91 mL) in a 2L flask was cooled on ice under nitrogen and then treated with benzyl triethyl ammonium chloride (2.0 g, 0.0088 mol, Aldrich) and (benzhydrylideneamino)acetonitrile (47.89 g) in toluene (100 mL). 1,2-Dibromoethane (23 mL, 122.4 mmol, Aldrich) was then added dropwise over 25 min to

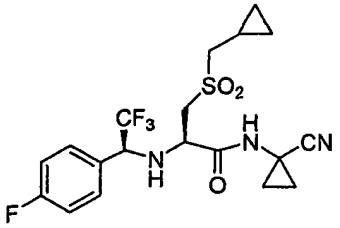
the reaction mixture with mechanical stirring and cooling to maintain the internal temperature near +10 °C. The reaction mixture was then stirred vigorously for 24 h at room temperature and then poured into ice water and the mixture was extracted with toluene. The combined extracts were washed with brine and then treated with $MgSO_4$ and Norite. After filtering, toluene was removed by rotary evaporation to give an oil (67 g). The residue was dissolved in boiling hexane (400 mL), treated with Norite and filtered hot and allowed to cool. A dark oil separated and which was removed by pipet (~2 mL). Scratching induced crystallization in the remaining solution which was cooled on ice for 2 h. Light yellow crystals were collected by filtration and washed with cold hexane to give 1-(benzhydrylideneamino)cyclopropanecarbonitrile (30.56 g).

Step 3

A mixture of 1-(benzhydrylideneamino)cyclopropanecarbonitrile (30.56 g, 0.124 mol) in concentrated HCl (12 mL) in water (100 mL) and ether (100 mL) was stirred at room temperature for 15 h. The ether layer was discarded and the aqueous layer was washed with ether. The aqueous layer was then freeze dried to give the title compound as a tan powder (13.51 g). This compound is also commercially available.

Example 1

Synthesis of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionamide



Step 1

A 12 L flask was charged with dichloromethane (3.7 L) and 2,2,2-trifluoro-1(*R*) -(4-fluorophenyl)ethanol (367 g; 1.89 mol, 90% ee) was added. The reaction mixture was cooled to an internal temperature of –50 °C and *N,N*-diisopropylethylamine (DIPEA; 855 g, 1153 mL, 6.62 mol, 350 mole%) was added while the solution was maintained at –50 °C. After the addition was complete, trifluoromethanesulfonic anhydride (560 g, 334 mL, 1.98 mol, 105 mole%) was added via an addition funnel over 0.75 h, maintaining the solution at -50±5 °C and the solution was stirred at that temperature for 4-6 h, by which time formation of the triflate

was determined to be complete by ^{19}F-NMR analysis. Solid S-trityl-L-cysteine (686 g, 1.89 mol, 100 mole%) was added in one portion, causing the internal temperature of the solution to rise to -40 °C. The reaction mixture was allowed to warm to 10 °C overnight to give a homogenous solution. The reaction mixture was stirred for an additional 10 hours at 10 °C, by which time no further reaction had taken place as determined by HPLC analysis. Toluene (5 L) was added, followed by removal of the dichloromethane *in vacuo*. The precipitated trifluoromethanesulfonic acid salt of DIPEA was removed by filtration. The filtrate was washed with 2N aqueous HCl (4 L), followed by saturated aqueous NaCl (4 L). The resulting toluene solution was concentrated to give 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid and 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid as a 5:1 mixture and 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid 2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethyl ester and 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid 2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethyl ester as side products. The crude material was taken onto the next step without any additional purification.

Step 2

A crude mixture of 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid and 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-trityl-sulfanylpropionic acid (430 g; 797 mmol) from step 1 above, was dissolved in dichloromethane (310 mL) and TFA (238 mL; 352 g; 3.09 mole; 388 mole%) and the solution was cooled in an ice water bath. Triethylsilane (247 mL; 180 g; 1.55 mol; 194 mole%) was added dropwise. After the addition was complete, the ice-bath was removed and the reaction mixture was allowed to warm up to room temperature. After stirring for an additional 1 hour, HPLC-MS analysis showed the reaction was complete. The dichloromethane was removed *in vacuo*. The concentrated material was diluted with toluene (300 mL) and the mixture was concentrated *in vacuo* to remove volatile residues (triethylsilane and TFA). The azeotropic distillation process was repeated by the addition of another portion of toluene to the crude product. The resulting dark residue was diluted with hexane (800 mL) and the mixture was extracted with a 3N NaOH solution (500 mL) and then a 2N NaOH solution. The combined, basic (pH > 13) aqueous extracts were washed with hexane and then treated with tris(2-carboxyethyl)phosphine•HCl (22.1 g; 77.1 mmol; 9.7 mole%) and cyclopropylmethyl bromide (104.6 g; 775 mmol). The reaction mixture was stirred, keeping the mixture basic (pH > 13) with the addition of 3N aqueous NaOH solution. After 2 h, HPLC analysis showed the reaction to be complete. The reaction mixture was acidified to pH 2-3 with concentrated

aqueous HCl and extracted twice with diethyl ether. The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated *in vacuo* to give 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionic acid and 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)-ethylamino]propionic acid (193 g, 68.9 %) as a dark oil.

Step 3

A mixture of 3-cyclopropylmethanelsulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]-propionic acid and and 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)-ethylamino]propionic acid (193 g; 549 mmol) was dissolved in *N*-methylpyrrolidinone (NMP; 1 L) and 1-amino-1-cyclopropylcarbonitrile (65.2 g; 550 mmol), HATU (209.1 g; 550.0 mmol) and DIPEA (239.6 mL; 177.8 g; 1.37 mol; 250 mole%) were added to the solution under ice-bath cooling. After addition was complete, the ice-bath was removed and the reaction mixture was warmed to room temperature. After 2 h, LC-MS analysis showed the reaction to be complete. OXONE ® (507.8 g; 826 mmol; 150 mole%) was dissolved in hot (60-70 °C) water (1.25 L) and the resulting solution was added to the reaction mixture at such a rate so as to maintain the internal temperature ≤50 °C. After 1 h, the reaction was complete and water (2 L) was added. The resulting slurry was stirred for 1h, filtered and the resulting solid was washed with water (1 L) and then 2-propanol (IPA) (500 mL). The solid was air-dried to give 145 g of a powder, which was dissolved in ethyl acetate (1.5 L) and the resulting solution washed with water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give crude product (127 g), which was dissolved in hot (85-90 °C) IPA (2.5 L). The solution was placed in a hot water bath (70 °C) for crystallization, decreasing the temperature of the water bath by 15 °C per hour. Crystallization was observed at 50 °C. After having cooled to room temperature, the crystals were filtered and washed with IPA, then dried under vacuum oven at 65 °C for 24 h to afford the title compound (87 g) having Form A by XRPD analysis.

Alternate preparation:

Step 1

To a 1.25 L of the crude product from Example 1, step 1 above containing 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]-3-tritylsulfanylpropionic acid, 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)-ethylamino]-3-tritylsulfanylpropionic acid, 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid 2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethyl ester and 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid 2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethyl ester (193 g product

yield) was added isopropanol (300 mL), followed by 10% aqueous solution of lithium hydroxide (300 mL) to give pH 14. The reaction mixture was stirred overnight until 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid 2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethyl ester and 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid 2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethyl ester was converted to the corresponding acids as determined by HPLC-UV analysis. The solution was then acidified to pH 3 with concentrated HCl, then loaded onto a pad of silica gel (5" x 6") and eluted with ethyl acetate. The filtrate was concentrated *in vacuo* to give an oil, which was dissolved in dichloromethane (1.5 L). The solution was stirred then heptane (800 mL) was added. Most of the dichloromethane was removed by distillation at 60 °C and replaced with additional heptane (800 mL). Stirring was continued and the reaction mixture was allowed to cool to room temperature overnight. The resulting precipitated solid was filtered and washed with heptane to give 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid and 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid (207 g) as a 12:1 diastereomeric mixture.

Step 2

A solution of 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid and 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanyl-propionic acid (207 g; 384 mmol) in dichloromethane (400 mL) was cooled to 10 °C and trifluoroacetic acid (118 mL) was added, followed by the dropwise addition of triethylsilane (122 mL), maintaining the internal temperature below 30 °C. After the reaction was complete (2 h), the reaction mixture was concentrated *in vacuo* and then the residue was co-evaporated from toluene. The residue was dissolved in dichloromethane (500 mL) and this solution was extracted with 10% aqueous NaOH. The aqueous extract was washed with dichloromethane (100 mL) then the aqueous phase was treated with tris-(2-carboxylethyl-phosphine) (11.0 g; 38.4 mmol), followed by cyclopropylmethyl bromide (52.0 g; 385 mmol). The resulting solution was stirred overnight then dichloromethane (400 mL) was added and the reaction mixture cooled to 10 °C. The reaction mixture was acidified to pH 3-4 with concentrated HCl (35 mL). The layers were separated and the organic phase was washed with water (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. The oil was dissolved in ethyl acetate (500 mL) and filtered through a 4" x 3" pad of silica gel, eluting with ethyl acetate (1.5 L). The filtrate was concentrated *in vacuo* to give 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]propionic acid (100 g) as an oil.

Step 3

To a solution of 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluoro-phenyl)ethylamino]propionic acid (50.0 g; 142 mmol) in *N*-methylpyrrolidine (NMP; 260 mL) was added 1-amino-1-cyclopropanecarbonitrile hydrochloride 7; (17.5 g; 148 mmol; 104 mole%) followed by HATU (56.0 g; 147 mmol), and *N,N*-diisopropylethylamine (62.0 mL; 46.0 g; 356 mmol; 250 mol%). The internal temperature was below 24 °C. The reaction was stirred at room temperature and the progress of the reaction was monitored by HPLC and LC-MS. After 3 h, HPLC analysis showed an excess of starting material. Additional DIPEA (30 mL; 22.3 g; 172 mmol) was added to increase the pH from 3 to 10. No appreciable conversion was observed after an additional 1 hour reaction time. An additional 10% (5.6 g; 14.7 mmol) of HATU was added and the reaction was complete after 1 h, as determined by LC-MS analysis.

The reaction mixture was diluted with NMP (100 mL) and the mixture was treated with a solution of OXONE ® (157 g; 255 mmol; 180 mole%) in water (360 mL) which was prepared by heating at 70 °C, then cooled to 45 °C for the addition. Addition of the aqueous solution of OXONE ® afforded a suspension that was difficult to stir. The slurry was stirred overnight at which time, LC-MS showed the reaction to be complete. The reaction mixture was diluted with water (500 mL) and the resulting suspension stirred for an additional 30 minutes. The solids were filtered and washed with water (500 mL) and then isopropanol (250 mL). The filter cake was dissolved in ethyl acetate (1.5 L) and the solution washed with water (1.5 L), water (500 mL), and saturated aqueous NaCl (500 mL). The organic phase was concentrated *in vacuo* to give 50 g of an off-white solid. The solid was dissolved in a mixture of isopropanol (500 mL) and water (50 mL) in an oil bath at 90 °C then the solution was allowed to cool overnight with stirring. A thick white crystalline solid was produced which was diluted with isopropanol (200 mL) to aid in transfer for filtration. The solid was filtered, washed with isopropanol (200 mL), air-dried then dried *in vacuo* to give the title compound (42.0 g) as a crystalline solid.

Alternate preparation of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide:

Step 1

Neat cyclopropylmethyl bromide (45g) was added to a vigorously stirring ice water bath cooled solution of L-cysteine (40.32 g) in 2N NaOH (26.6g in 333mL water). The reaction mixture was stirred in the ice water bath for 3 h and then neutralized to pH 6 with 6N HCl. The precipitated product was collected by vacuum filtration and was washed with

hexanes and further dried by lyophilization to yield 2-(*R*)-amino-3-cyclopropylmethanesulfanylpropionic acid (58 g) as a white solid.

Step 2

Lithium aluminum hydride (200 mL, 1.5M solution in tetrahydrofuran) was cooled in an ice bath and solid 2-(*R*)-amino-3-cyclopropylmethanesulfanylpropionic acid (20 g) was added by tapping into the flask through a powder funnel to control gas evolution. Once the addition was complete, the bath was removed and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled in an ice bath and diethyl ether (110 mL) was added followed by dropwise addition of 5 mL water, 5mL 15% aq. NaOH, and then 15mL more water. Stirring in the ice bath was continued for 2 h, and then the reaction mixture was vacuum filtered. The filter cake was washed with diethyl ether portions. The filtrate was dried over anhydrous Na_2SO_4 and concentrated to give 2(*R*)-amino-3-cyclopropylmethanesulfanylpropan-1-ol (15.03 g) as a colorless oil.

Step 3

A solution of 2(*R*)-amino-3-cyclopropylmethanesulfanylpropan-1-ol (15.03 g) and trifluoroacetaldehyde methyl hemiacetal (12.2 g) in toluene (100 mL) was heated at reflux with Dean Stark trapping of water for 24 h. The reaction mixture was concentrated to give 4-cyclopropylmethanesulfanylmethyl-2-trifluoromethyloxazolidine (17.61 g) as a pale yellow oil.

Step 4

Part A. A solution of 4-cyclopropylmethanesulfanylmethyl-2-trifluoromethyloxazolidine (17.6 g) in anhydrous tetrahydrofuran (145 mL) was cooled in an ice water bath and treated with chlorotrimethylsilane (11 mL) and lithium bis(trimethylsilyl)amide (87.5 mL of 1.0M solution in tetrahydrofuran). The reaction mixture was allowed to stir under ice bath cooling for 30 min and then at room temperature for 1 h.

Part B. A solution of 4-fluorobromobenzene (24 mL) in anhydrous tetrahydrofuran (440 mL) was cooled to –78 °C and then treated with *n*-butyllithium (137 mL of 1.6M solution in hexanes). After 20 minutes, the solution from Part A was transferred by cannula to this mixture at –78 °C over 10 minutes. Stirring at –78 °C for 2 hours was followed by addition of 1N HCl (300 mL) and then the reaction mixture was allowed to warm to room temperature. The crude product was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, concentrated, and chromatographed using an 8:1 to 5:1 gradient of hexane:ethyl acetate to give 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1*S*-(4-fluoro-phenyl)ethylamino]propan-1-ol (13.0 g) and a mixed fraction comprising a

mixture of 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1*S*-(4-fluorophenyl)ethylamino]propan-1-ol and 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1*R*-(4-fluorophenyl)ethylamino]propan-1-ol (5.23 g), and 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1*R*-(4-fluorophenyl)-ethylamino]propan-1-ol (1.5 g).

Step 5

Solutions of 0.41M periodic acid in dry acetonitrile and 0.02M chromium trioxide in dry acetonitrile were prepared 3 h ahead, with stirring at room temperature. Periodic acid solution (477 mL) was chilled in an ice/acetone bath and treated first with chromium trioxide solution (95 mL), then a solution of 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1*S*-(4-fluoro-phenyl)ethylamino]propan-1-ol (13 g) in acetonitrile (85 mL). The reaction was monitored by TLC (1%acetic acid in 1:1 hexanes:ethyl acetate) and portions of the chromium trioxide solution were added (95 mL at 1.5 h reaction time, 40 mL at 4.5 h reaction time). After 1 more hour reaction time, the reaction was complete by HPLC analysis. Isopropanol (200 mL) was added and the reaction mixture was allowed to warm to room temperature and then was concentrated. The resulting solids were partitioned between ethyl acetate and saturated aqueous KH_2PO_4. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Solvent was removed and *tert*-butyl methyl ether (60 mL) was added followed by dicyclohexylamine (4 mL). The mixture reaction was stored in the freezer overnight. Some salt crystallization had occurred. Hexane was added in 5 mL portions to a total of 60 mL and the reaction mixture was stored in the freezer overnight. The supernatant was decanted. The supernatant yielded several crops of dicyclohexylamine salt, 4.89 g in total. This salt was partitioned between 2N aq HCl and ethyl acetate, and the ethyl acetate layer was concentrated to give 3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1*S*-(4-fluorophenyl)ethylamino]propionic acid (3.29 g).

Step 6

A mixture of 3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1*S*-(4-fluorophenyl)-ethylamino]propionic acid (3.29 g), 1-aminocyclopropanecarbonitrile hydrochloride (1.33 g), HATU (4.6 g) and dimethylformamide (20 mL) was treated with diisopropylethylamine (3.4 mL) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with 1N HCl, water, saturated sodium bicarbonate solution, and brine, and then was dried over $MgSO_4$, filtered and concentrated. The crude product was chromatographed using 1:1 hexane:ethyl acetate and further purified by recrystallization from hot ethyl acetate to give *N*-(1-

cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)-propionamide (2.44 g) as a colorless crystalline solid. XRPD analysis showed it to be about a 90:10 mixture of Forms A and C.

Alternate preparation of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-(2,2,2-trifluoro-1(*S*)-4-fluorophenylethylamino)propionamide:

Step 1

Sodium hydride, 60% dispersion in mineral oil (10.53 g, 0.263 mol) was added to a dried 500 mL flask and washed twice with dried hexane (50 mL). After adding dry ether ether (100 mL), a solution of 2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethanol (39.3 g, 0.203 mol, 90% ee) in ethyl ether (100 mL) was added at 0° C and the reaction mixture was allowed to warm up to room temperature and stirred for 2 h. The reaction mixture was cooled to 0° C and a solution of trifluoromethanesulfonyl chloride (44.24 g, 0.263 mol) in ethyl ether (50 mL) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. After removing the solvent, the residue was diluted with hexane (500 mL) and washed with a saturated $NaHCO_3$ solution and brine. After drying with $MgSO_4$, the solvent was removed on roto-vap to give trifluoromethanesulfonic acid 2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethyl ester (62.83 g) as a colorless oil which was used in the next step without further purification.

Step 2

Into a stirred suspension of S-trityl-L-cysteine (70 g, 0.193 mol) in dichloromethane (800 mL) was added DIPEA (74.55 g, 0.578 mol) and 2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethyl ester (62.8 g) at 25° C. After 20 h, the solvent was removed and the residue was diluted with ethyl ether (800 mL) and washed with 1N HCl. After drying with $MgSO_4$, the solvents were removed on rot-vap to give 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid and 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)ethylamino]-3-tritylsulfanylpropionic acid (110 g). ^{1}HNMR shows the product to be a mixture of diastereomer (9:1).

Step 3

Into a 2L flask charged a (9:1) mixture of 2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]-3-tritylsulfanylpropionic acid and 2(*R*)-[2,2,2-trifluoro-1(*R*)-(4-fluorophenyl)-ethylamino]-3-tritylsulfanylpropionic acid (109 g) in dichloromethane (150 mL) and TFA (89.6 g) was added triethylsilane (45.6 g) under ice-bath cooling. After addition was completed, the ice-bath was removed and the reaction mixture allowed to warm up to room temperature. After 1 h, HPLC-MS showed the reaction was complete. After removing the solvent, the residue was diluted with 1N NaOH (500 mL) and extracted with hexane. To the

water phase, dioxane (250 mL), tris(2-carboxyethyl)phosphine-HCl (5.5 g) and cyclopropylmethylbromide (26 g) were added. After 12 h, HPLC shows the reaction was completed. Dioxane was removed and the reaction mixture was acidified with concentrated HCl to pH 2-3 and extracted with ethyl ether. The combined ethyl ether layers were washed with brine, dried over $MgSO_4$ and concentrated to give 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]-propionic acid (38.86 g) as a dark oil.

Step 4

Into a solution of 3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)-ethylamino]propionic acid (38.8 g) in DMF (100 mL) was added 1-aminocyclopropane-carbonitrile hydrochloride (15.1 g), HATU (48.3 g), and DIPEA (55.4 mL) under ice-bath cooling. After addition was complete, ice-bath was removed and the reaction mixture allowed to warm up to room temperature. After 2 h, HPLC showed the reaction was completed. The reaction mixture was diluted with 1L ethyl ether and washed with saturated $NaHCO_3$ solution and brine. After drying with $MgSO_4$, the solvent was removed to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (41.4 g) as a brown oil.

Step 5

N-(1-Cyanocyclopropyl)-3-cyclopropylmethanesulfanyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)-ethylamino]propionamide was dissolved in methanol (400 mL) and a solution of OXONE® (88.9g) in hot water (400 mL) was added. After 1 h, methanol was removed on roto-vap., and the residue was extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$, filtered and the filtrated was concentrated to give crude product (46.73 g) as a white solid LC-MS showed the product contained 7.8% of sulfoxide. The crude product was redissolved in methanol (500 mL) and a solution of OXONE® (18 g) in water (300 mL) was added. After 1 h, the reaction mixture was worked up as described above to give crude product (100 g) which was crystallized from ethyl acetate and hexane to give the title compound (27. 5 g).

The above procedure was repeated twice to prepare 28 g and 33 g batches of the title compound. The batches were combined and crystallized from isopropanol at 80-90° C to give crystalline product (76 g) as pure Form A (by XRPD analysis) and additional 4.5 g of title compound as Form A with about 10% Form B.

Processes for the preparation of polymorphoic forms of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide.

Form A:

(i) A suspension of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]propionamide (1.0023 g) (Form A with some Form B or C) in 2-propanol (30 mL) was heated to 80 °C to generate a clear solution. The solution was filtered through 0.2 μm filter into a pre-warmed flask. Water (3.0 mL) was added and the solution remained clear. The flask was placed into a water bath for controlled cooling from 80 to 5 °C at a rate of 5 °C/h. After about 23 h, white crystals were collected by filtration. The solids were dried under vacuum for 2 h to give *N*-(1-cyanocyclopropyl)-3-cyclopropyl-methanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (0.84 g) as pure Form A.

(ii) Ethanol (1.5 mL) was added to *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (29.3 mg) (Form A with some Form B or C). The solution was heated to reflux on a hot plate. A clear solution was obtained. The solution was filtered through a pre-warmed syringe and 0.2 μm nylon syringe filter. The filtrate was collected in a pre-warmed vial. The vial was placed on a hot plate and heating turned off to allow slow cooling. The solids were collected by vacuum filtration to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide as pure Form A.

(iii) A 2:1 by volume acetonitrile:water solution was prepared and *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (Form A with some Form B or C) was added. The vial was capped and placed onto a 60 °C hot plate to give a clear solution. Additional amount of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide was added to the above solution. The solution was then filtered with a 0.2 μm nylon filter into a warm receiving vial and capped. The hot plate was shut off and the solution was allowed to slowly cool to room temperature. The precipitates were filtered and allowed to air dry to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide as pure Form A.

(iv) *N*-(1-Cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (Form A with some Form B or C) was dissolved in acetone to give a clear, light yellow solution. The solution was filtered with a 0.2 μm nylon filter into a 2-dram vial and covered with foil. A single hole was made in the foil to allow for slow evaporation. Solvent was evaporated completely to yield *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-

propionamide as pure Form A.

(v) *N*-(1-Cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (Form A with some Form B or C), was added in methylene chloride and placed onto a 45 °C hot plate. Solids were present in a clear, light yellow solution. The solution was filtered with 0.2 μm nylon filter into a warm receiving vial. The vial was capped and the hot plate was turned off. The sample was allowed to slowly cool to room temperature. The solids were collected by vacuum filtration to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)-ethylamino]-propionamide as pure Form A.

(vi) *N*-(1-Cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (24.4 mg) (Form A with some Form B or C) was added to toluene (500 μL). The solution was heated to approximately 100 °C on a hot plate. A clear solution was obtained. The solution was filtered through a pre-warmed syringe and 0.2 μm nylon syringe filter. The filtrate was collected in a pre-warmed vial. The vial was placed on a hot plate and heating turned off to allow slow cooling. The solids were collected by vacuum filtration to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide as pure Form A.

Form B:

N-(1-Cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide (20.6 mg), predominately Form A, was added to trifluoroethanol (1.5 mL) and the mixture was heated to approximately 80 °C. A clear solution was obtained, which was then filtered. The filtered solution was cooled on a hot plate from 80 °C to 55 °C at a rate of 1 °C /h. No solids were present at this point, and the sample was placed in the refrigerator. After the sample was removed from the refrigerator, solids were immediately collected by filtration and allowed to air dry to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide as a mixture of Form A and B. XPRD analysis showed the amount of Form B in the product was about 90%.

Form C:

A small quantity of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide Form A was placed into a stainless steel container with a single stainless steel ball. The material was ground for 20.0 minutes at 30 s^{-1} frequency on a Retsch mixer mill to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethane-sulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-

propionamide as pure Form C.

Form D

(i) A small amount of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide Form A material was packed into an Inel capillary tube. The capillary tube was then placed in the melting point apparatus and heated at approximately 10 °C/minute to 170 – 171 °C. Heating was then continued to 200 °C. The capillary tube was then removed from the melting point apparatus and placed immediately in a liquid nitrogen bath to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide as Form D. XPRD analysis showed the amount of Form D in the product was about 90% pure.

(ii) A small amount of *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide Form A material was placed in a stainless steel cylinder, equipped with a stainless steel rod and capped. The sample was ground in a SPEX/Certiprep model 6750 freezer mill filled with liquid nitrogen. The program was set for two minute grinding cycles with cooling in between each grinding. The cycle was repeated 10 times for a total grinding time of 20 minutes. The sample was then placed in a desiccator and allowed to equilibrate to ambient temperature for 30 minutes to give *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-4-(fluorophenyl)ethylamino]-propionamide as Form D. XPRD analysis showed the amount of Form D in the product was about 90%.

The polymorphic purity of the compound of Formula (I) was determined using XRPD analysis which has a detection error of about 3%. It should be understood that other more sensitive spectroscopic methods such as Raman Spectroscopy and solid state NMR could be used to determine the polymorphic purity of the compounds of the invention more precisely.

Biological Examples

Example 1

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); β-mercaptoethanol, 2.5 mM; and BSA, 0.00%. Human cathepsin S (0.05 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for

30 min at room temperature. Z-Val-Val-Arg-AMC (4 nMoles in 25 μL of assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (at λ 460 nm) for 5 min. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Example 2

In vitro Iip10 accumulation assay

During normal antigen presentation, Iip10 is proteolytically degraded to enable loading of a peptide fragment and subsequent MHC-II presentation on the surface of antigen presenting cells. The cleavage process is mediated by Cathepsin S. Thus, the Iip10 assay is an *in vitro* measure of a compound's ability to block cathepsin S and by extension antigen presentation. A compound that causes the accumulation of Iip10 at low concentration would be expected to block presentation of antigens.

Method:

Raji cells (4×10^6) were cultured with 0.02% DMSO or different concentrations of Cathepsin S inhibitors in RPMI medium 1640 containing 10 % (v/v) FBS, 10 mM HEPES, 2 mM L-glutamine, and 1 mM sodium pyruvate for four h at 37°C in 5% CO_2 humidified atmosphere. After the culture period, cells were washed with cold PBS and cells were then lysed in NP-40 lysis buffer (5 mM EDTA, 1% NP-40, 150 mM NaCl, and 50 mM Tris, pH 7.6) with protease inhibitors. Protein determinations were performed and lysate samples were boiled in reducing SDS sample buffer. Proteins were separated by electrophoresis on 12% NuPAGE® Bis-Tris gels. Proteins were then transferred to nitrocellulose membranes, and after incubation with blocking buffer (5% non-fat dry milk in PBS-Tween), the blots were incubated with the primary antibody against human CD74 invariant chain synthetic peptide (1.5 to 2 μg/mL of mouse anti-CD74 monoclonal antibody, PIN.1, Stressgen Biotechnologies). Blots were then incubated with the secondary antibody, horseradish peroxidase conjugated donkey anti-mouse IgG, at a 1:10,000 dilution. Immunoreactive proteins were detected by chemiluminescense reaction using Pierce Super Signal® West Pico chemiluminescense substrate.

FORMULATION EXAMPLES

Example 1

Representative pharmaceutical formulations Containing a Compound of Formula (I)

ORAL FORMULATION

SUSPENSION FORMULATION

Form A	1 – 100 mg
Xanthan Gum	2.5 mg
Tween 80	5 mg
Sucrose	100 mg
Sorbic acid	1 mg
Methylparaben	1.8 mg
Propylparaben	0.2 mg
Water	1 mL

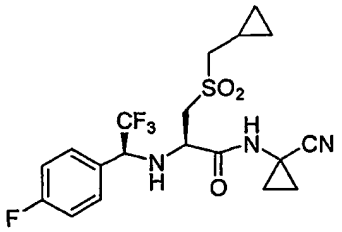
TABLET FORMULATION

Compound of Formula (I)	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

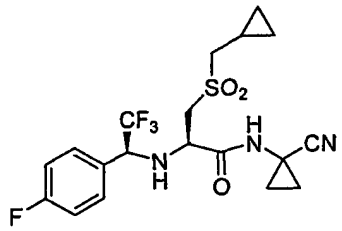
WE CLAIM:

1. A compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 19.47, and 21.67° (2-theta) (Form A).

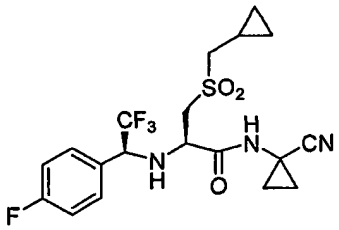
2. A compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 8.52, 9.15, 14.42, 17.67, 18.79, 19.47, 19.74, 21.67, 23.16, 23.89, 25.3 1, and 27.06° (2-theta); and

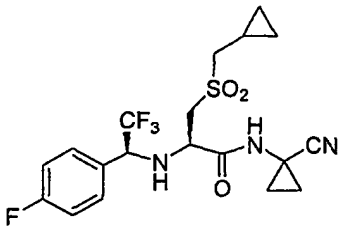
FT-IR spectrum with peaks at about 704, 731, 777, 791, 808, 822, 837, 856, 892, 921, 935, 987, 1008, 1028, 1053, 1080, 1115, 1128, 1161, 1180, 1230, 1261, 1288, 1361, 1418, 1465, 1513, 1548, 1607, 1663, and 3349 cm^{-1} (Form A).

3. A compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having a characteristic peak at about 5.65° (2 theta) (Form B).

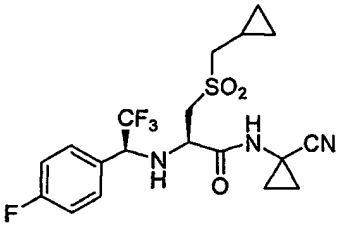
4. A compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having a characteristic peak at about 5.65, 6.68, 10.12, 18.63, 19.40, 20.66, 21.47, 21.93, 22.47, 23.78, 25.52, 25.76, and 26.79° (2-theta) and

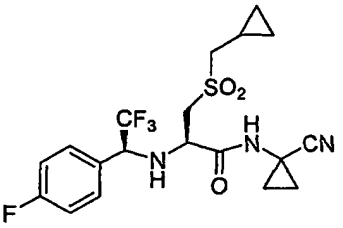
FT-IR spectrum peaks at about 704, 731, 791, 808, 823, 837, 856, 893, 936, 1028, 1053, 1080, 1115, 1128, 1 161, 1180, 1230, 1287, 1361, 1418, 1465, 1514, 1548, 1607, 1663, and 3349 cm^{-1} (Form B).

5. A compound of Formula (I):



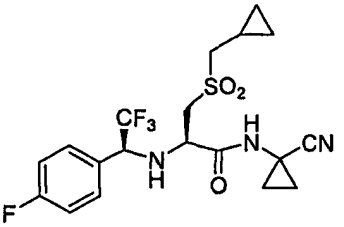
having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.24 and 7.50° (2-theta) (Form C).

6. A compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having broad peaks between about 5 and 12 and about 14 and 25° (2-theta) (Form D).

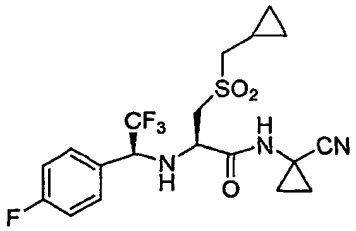
7. A pharmaceutical composition comprising a compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 19.47, and 21.67° (2-theta) (Form A) and a pharmaceutically

acceptable excipient.

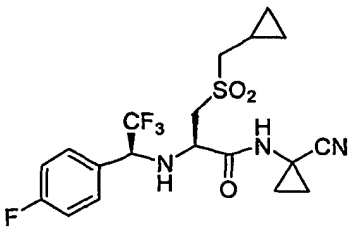
8. A pharmaceutical composition comprising a compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 8.52, 9.15, 14.42, 17.67, 18.79, 19.47, 19.74, 21.67, 23.16, 23.89, 25.31, and 27.06° (2-theta); and

FT-IR spectrum with peaks at about 704, 731, 777, 791, 808, 822, 837, 856, 892, 921, 935, 987, 1008, 1028, 1053, 1080, 1115, 1128, 1161, 1180, 1230, 1261, 1288, 1361, 1418, 1465, 1513, 1548, 1607, 1663, and 3349 cm^{-1} (Form A) and a pharmaceutically acceptable excipient.

9. A pharmaceutical composition comprising a compound of Formula (I):

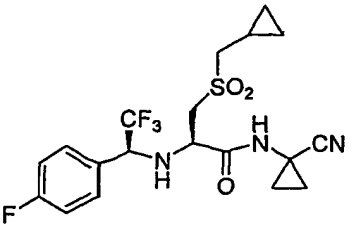


that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 19.47, and 21.67° (2-theta) (Form A) and a pharmaceutically acceptable excipient.

10. The pharmaceutical composition of Claim 9 wherein Form A is present in an amount greater than 95%.

11. The pharmaceutical composition of Claim 9 wherein Form A is present in an amount greater than 98%.

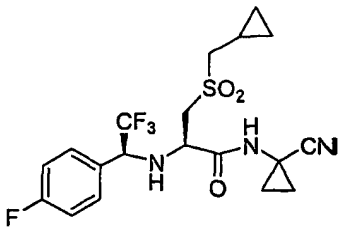
12. A pharmaceutical composition comprising a compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having

characteristic peak at about 5.65° (2 theta) (Form B) and a pharmaceutically acceptable excipient.

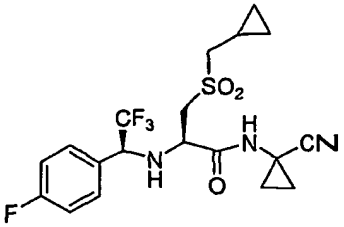
13. A pharmaceutical composition comprising a compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 5.65, 6.68, 10.12, 18.63, 19.40, 20.66, 21.47, 21.93, 22.47, 23.78, 25.52, 25.76, and 26.79° (2-theta) and

FT-IR spectrum peaks at about 704, 731, 791, 808, 823, 837, 856, 893, 936, 1028, 1053, 1080, 1115, 1128, 1161, 1180, 1230, 1287, 1361, 1418, 1465, 1514, 1548, 1607, 1663, and 3349 cm^{-1} (Form B)and a pharmaceutically acceptable excipient.

14. A pharmaceutical composition comprising a compound of Formula (I):

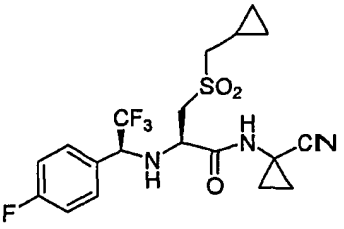


that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peak at about 5.65° (2 theta) (Form B) and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition of Claim 14 wherein Form B is present in an amount greater than 95%.

16. The pharmaceutical composition of Claim 14 wherein Form B is present in an amount greater than 98%.

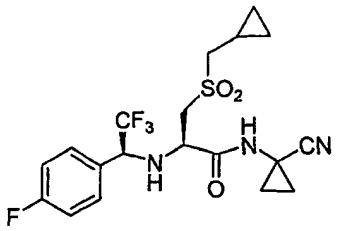
17. A pharmaceutical composition comprising a compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.24 and 7.50° (2-theta) (Form C) and a pharmaceutically

acceptable excipient.

18. A pharmaceutical composition comprising a compound of Formula (I):

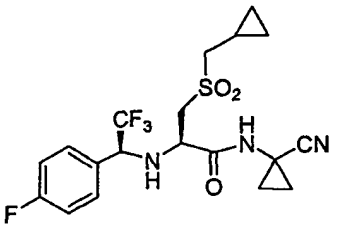


that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.24 and 7.50° (2-theta) (Form C) and a pharmaceutically acceptable excipient.

19. The pharmaceutical composition of Claim 18 wherein Form C is present in an amount greater than 95%.

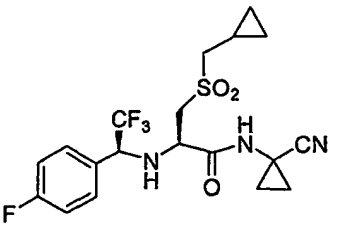
20. The pharmaceutical composition of Claim 18 wherein Form C is present in an amount greater than 98%.

21. A pharmaceutical composition comprising a compound of Formula (I):



having a polymorphic form which exhibits an X-ray powder diffraction pattern having broad peaks between about 5 and 12 and about 14 and 25° (2-theta) (Form D) and a pharmaceutically acceptable excipient.

22. A pharmaceutical composition comprising a compound of Formula (I):



that is in substantially pure polymorphic form which exhibits an X-ray powder diffraction pattern having broad peaks between about 5 and 12 and about 14 and 25° (2-theta) (Form D) and a pharmaceutically acceptable excipient.

23. The pharmaceutical composition of Claim 22 wherein Form D is present in an amount greater than 95%.

24. The pharmaceutical composition of Claim 22 wherein Form D is present in an amount

greater than 98%.

25. A method of treating a disease mediated by Cathepsin S which method in an animal which method comprises administering to the animal a pharmaceutical composition of any of the Claims 7-24.

26. A process for preparing a polymorph of the compound *N*-(1-cyanocyclopropyl)-3-cyclopropylmethanesulfonyl-2(*R*)-[2,2,2-trifluoro-1(*S*)-(4-fluorophenyl)ethylamino]-propionamide, said process comprising:

(a) solvent crystallization of the compound from a solvent or solvent mixture having sufficient chemical affinity to the compound without substantially affecting the two asymmetric centers of the compound during the crystallization process and isolation of the polymorph in substantially pure form; or

(b) crystallization of the compound by exposure to mechanical stress, compound particle size reduction, an electrical field or thermal treatment without substantially affecting the integrity of the compound or the two asymmetric centers of the compound during the crystallization process and isolation of the polymorph in substantially pure form; or

(c) liquefaction of the compound followed by rapid cooling of the liquefied compound or exposure of the compound to particle size reduction at temperatures below room temperature without substantially affecting the integrity of the compound or the two asymmetric centers of the compound during liquefaction or particle size reduction and isolation of the polymorph in substantially amorphous form.

27. The process of Claim 26, said process comprising a combination of steps (a) and (b).

28. The process of Claim 26, said process comprising step (a).

29. The process of Claim 26 or 28 wherein the isolated polymorph is Form A of the compound.

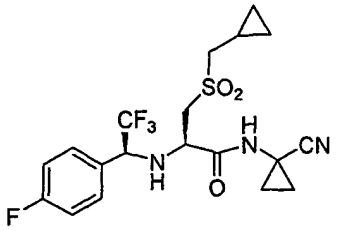
30. The process of Claim 29 wherein the solvent in step (a) is 2-propanol.

31. The process of Claim 26 wherein a first polymorph of the compound is converted to a second polymorph.

32. The process of Claim 31 wherein the first polymorph and the second polymorph have different thermodynamic stability.

33. The process of Claim 31 wherein the first polymorph has less thermodynamic stability than the second one.

34. A compound of Formula (I):



having a polymorphic form selected from the group consisting of:

(a) a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.19, 19.47, and 21.67° (2-theta) (Form A);

(b) a polymorphic form which exhibits an X-ray powder diffraction pattern having a characteristic peak at about 5.65° (2 theta) (Form B);

(c) a polymorphic form which exhibits an X-ray powder diffraction pattern having characteristic peaks at about 6.24 and 7.50° (2-theta) (Form C); and

(d) a polymorphic form which exhibits an X-ray powder diffraction pattern having broad peaks between about 5 and 12 and about 14 and 25° (2-theta) (Form D).

FIGURE 1

XRPD Pattern of Form A

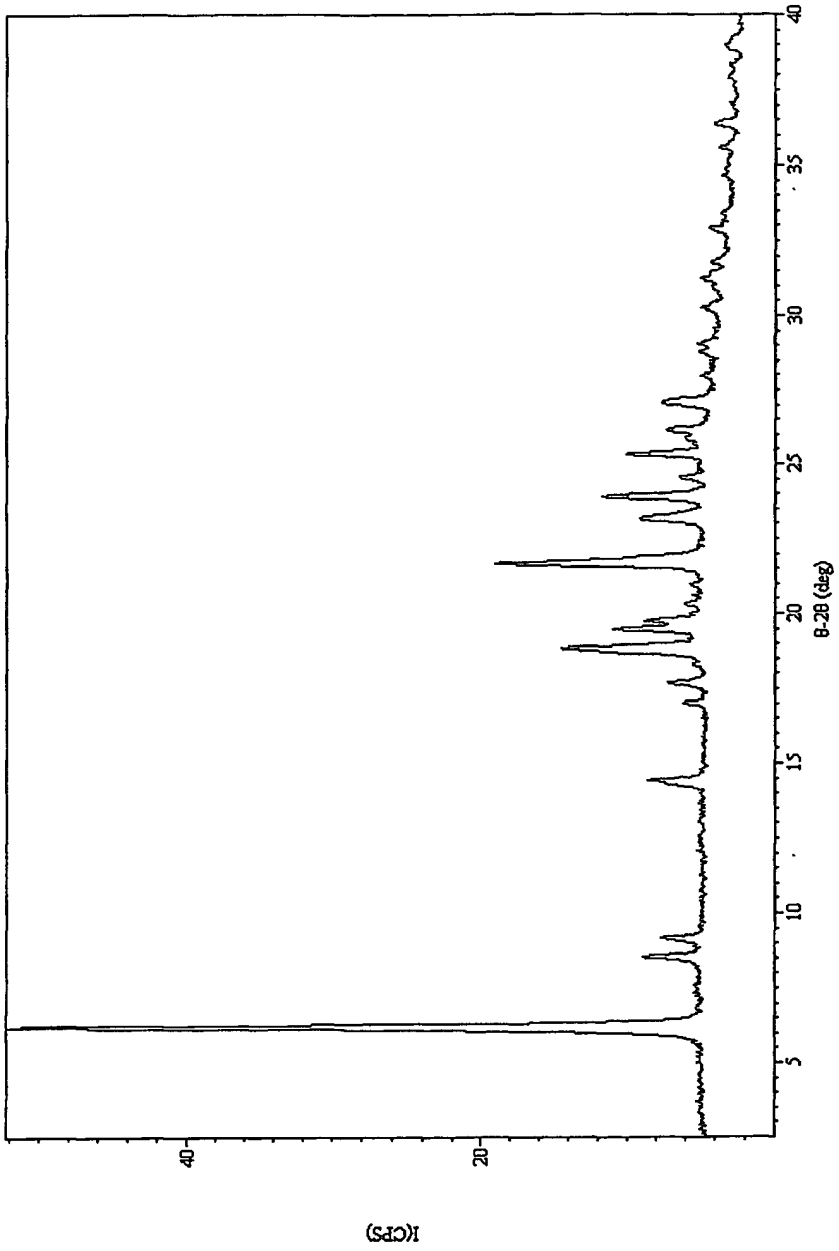
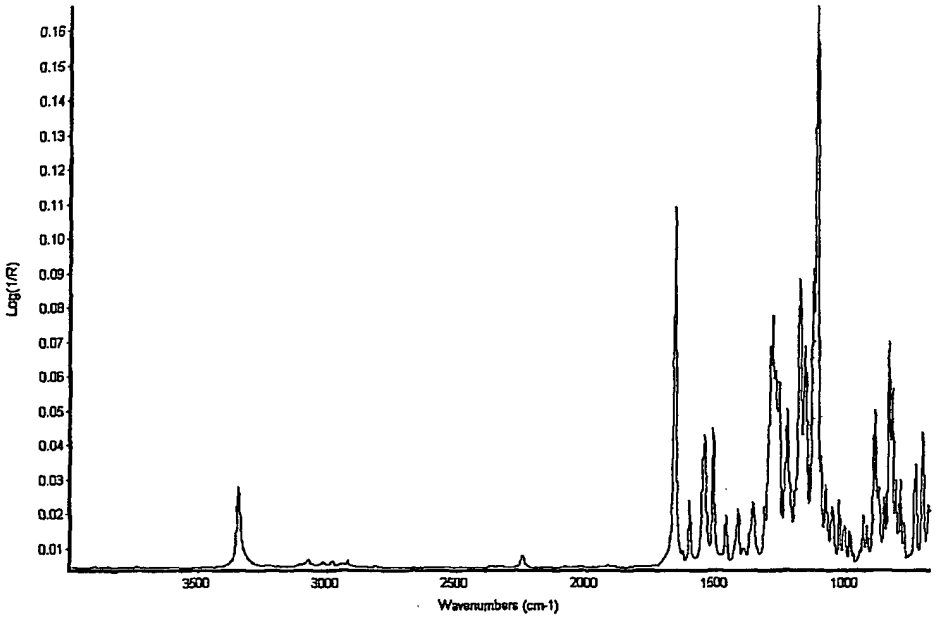


FIGURE 2

FT-IR Spectrum of Form A



FT-IR Spectrum of Form A with Labeled Peaks

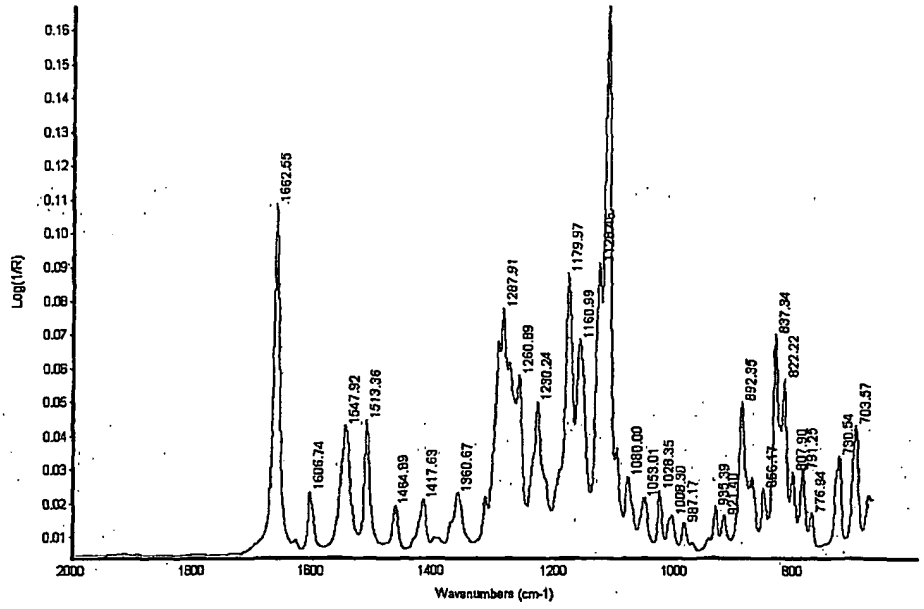


FIGURE 3

XRPD Pattern of Form B

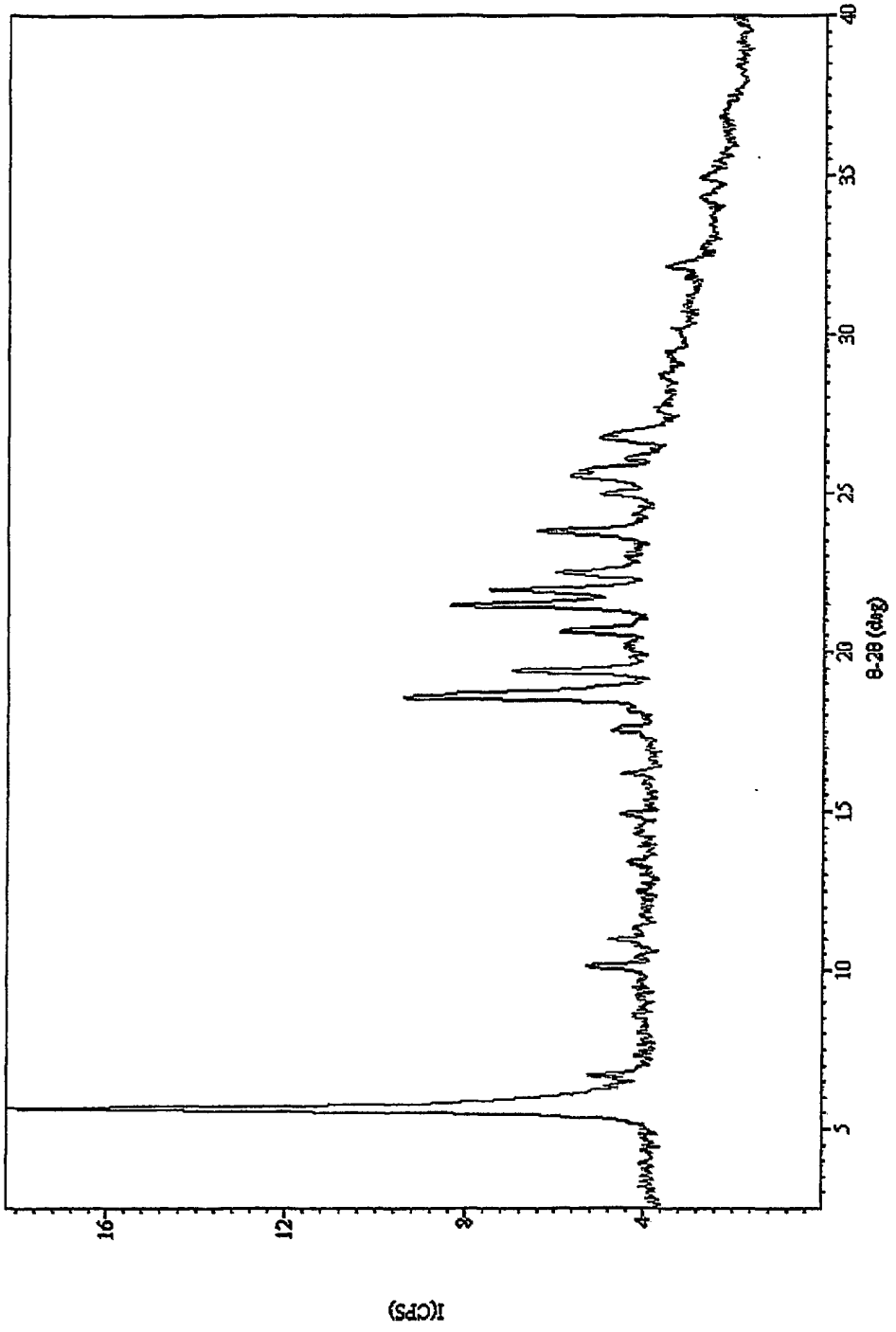
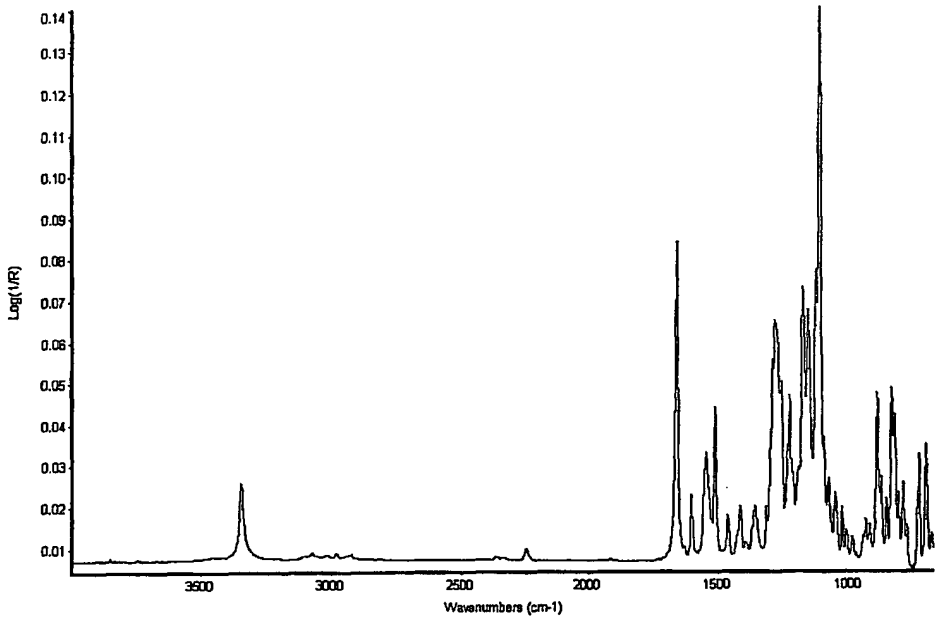


FIGURE 4

FT-IR Spectrum for Form B



FT-IR Spectrum of Form B with Labeled Peaks

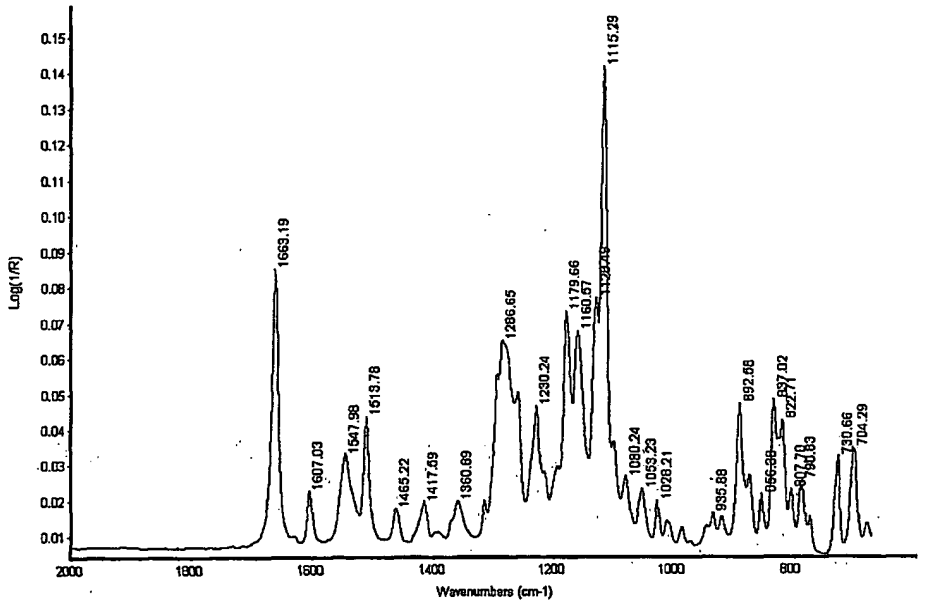


FIGURE 5

XRPD Pattern for Form C

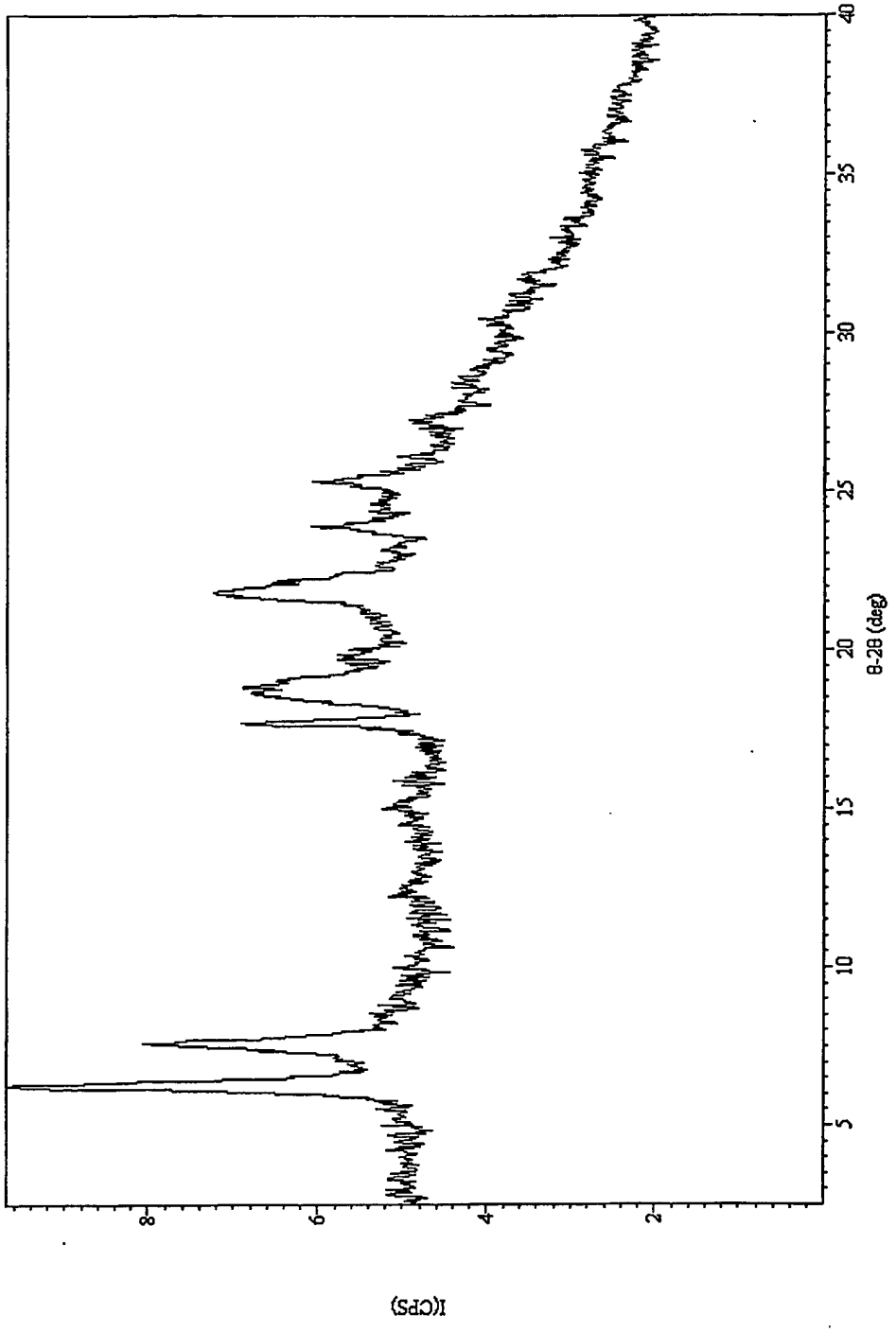
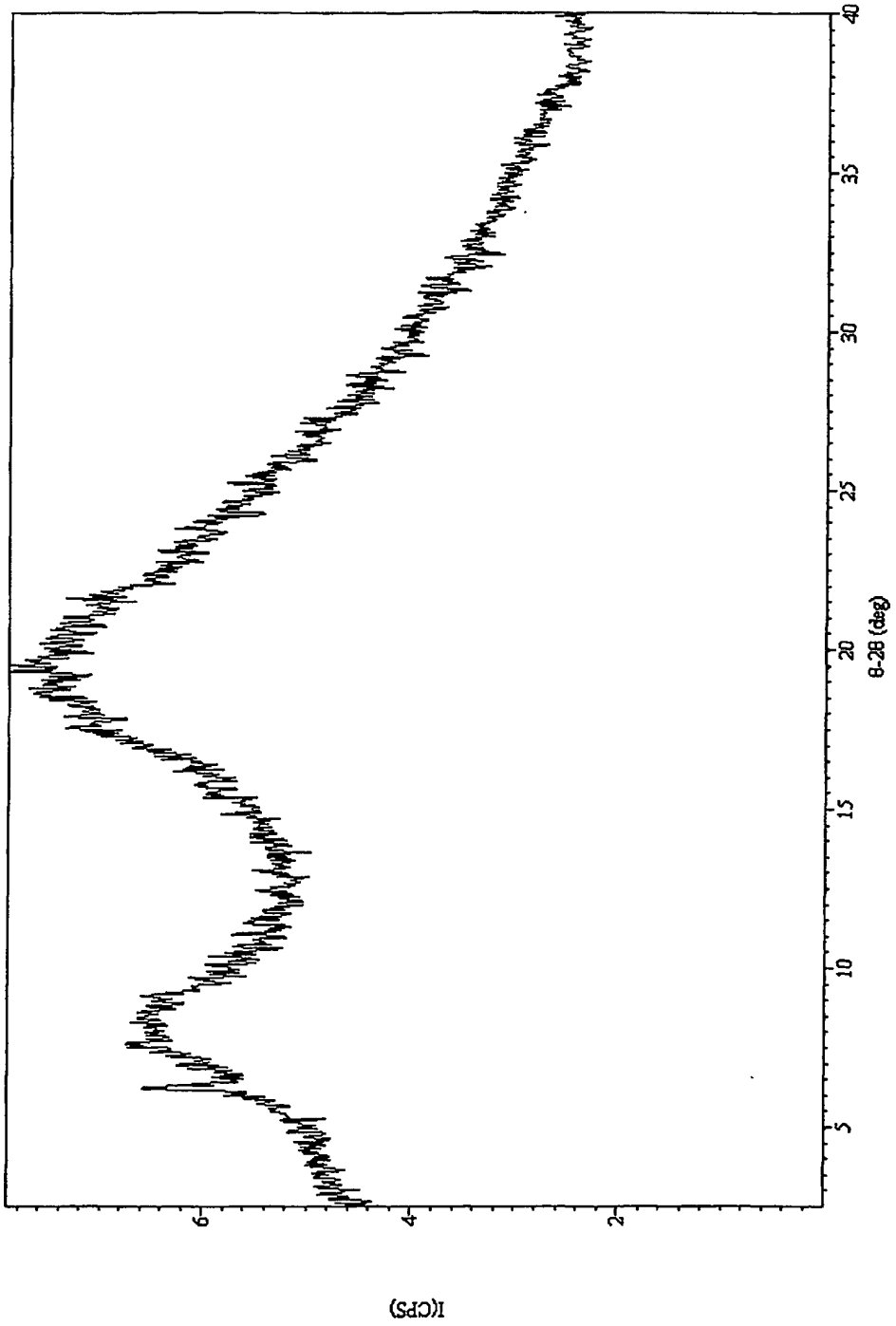


FIGURE 6

XRPD Pattern for Amorphous Form D



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/033074

A. CLASSIFICATION OF SUBJECT MATTER
C07C317/48 A61K31/277

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/028429 A (AXYS PHARMACEUTICALS, INC.) 31 March 2005 (2005-03-31) claims 25,30-32; examples 12,18	1-34

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2006	19/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kiernan, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/033074

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 25 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/033074

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005028429 A	31-03-2005	AU 2004274471 A1	31-03-2005
		CA 2521811 A1	31-03-2005